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Quantitative CT imaging analysis to predict pathology features in patients with a Congenital Pulmonary Airway Malformation

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ABSTRACT

Background: Risk for infection and potential malignant degeneration are the most common arguments for resecting asymptomatic Congenital Pulmonary Airway Malformations (CPAM). We aimed to investigate if CT- imaging characteristics can be used to predict histopathological features, by using an objective quantitative CT scoring method.
Methods: Archival CPAM tissue samples were histologically re-assessed and patients who had a pre-operative volumetric CT-scan were included. Lung disease was quantified using the newly-developed congenital lung abnormality quantification(CLAQ) scoring method and obtained percentages were used to predict histopathological signs of inflammation and presence of mucinous proliferation (MP). Because MP is presumed a precursor for mucinous adenocarcinoma *in situ* (AIS) this method was also used to compare CT-scans of patients with AIS to those with only CPAM.
Results: Thirty-three CPAM patients were included of which 13(39%) had histological signs of inflammation and 8(24%) had a MP. Patients with inflammation had a significantly smaller lesion (14% vs 38%) while those with MP had more extensive disease (54%vs17%). Patients with AIS had a significantly smaller lesion compared to CPAM patients (5%vs29%). Significant predictors for inflammation were smaller lesion size and percentage hypodensity within lesions while a larger lesion size and percentage parenchymal hyperdensity (solid lung tissue components) were predictors for MP as well as AIS.
Conclusions: Smaller CPAM lesions may be more susceptible to inflammation while larger lesions may be associated with the presence of MP. Parenchymal hyperdensity is found as a predictor for MP as well as AIS and should therefore elicit more extensive gross sampling.
Level of evidence: Level III.

1. Introduction

Due to a worldwide lack of consensus, no uniform management guidelines exist for the treatment of asymptomatic Congenital Pulmonary Airway Malformations (CPAM) [1–3]. These presumed rare CPAM are increasingly diagnosed prenatally due to the introduction of structural prenatal ultrasound screening programmes. Depending on the center or even on the specialist, patients with a CPAM are either monitored or undergo resection [4–6]. Arguments vary widely, but the most common reasons for resection are the risk of infection and malignant degeneration [4]. Identifying predictive features to aid in clinical decision making can be of added value to define the optimal management.

CPAM has an estimated incidence of 4 per 10,000 live births which is equal to other major congenital abnormalities such as congenital heart defects and neural tube defects [7,8]. Hence, it is possible that CPAM is more common than previously thought and that a part of the current adult population may have an undiagnosed, asymptomatic CPAM [9]. Consequently, the discussion on the optimal management is more relevant than ever. Approxi-

Abbreviations: AIS, (Mucinous) Adenocarcinoma *in situ*; CLA, Congenital lung abnormality; CLAQ, Congenital lung abnormality quantification; CONS, consolidation; CPAM, Congenital pulmonary airway malformation; CW, Cystic wall; CT, Computed tomography; LHyperD, Lesional hyperdensity; LHypoD, Lesional hypodensity; MP, Mucinous proliferation; PHyperD, Parenchymal hyperdensity; PHypoD, Parenchymal hypodensity.

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mately 3–10% of asymptomatic infants eventually develop respiratory distress or recurring infections and require a surgical resection [10–14].

Another reason for resection is the potential risk for malignant degeneration in CPAM [15–19]. In CPAM samples, mucinous proliferations (MP; *i.e.* clusters of mucinous cells), can be found in the lining of the cystic walls. This finding is presumed to be a precursor of mucinous adenocarcinoma *in situ* (AIS), previously known as bronchoalveolar carcinoma [15–20]. Identical gene mutations in AIS and MP further increase suspicion, although the exact pathogenesis remains unknown [15,17,21–23]. The risk for developing AIS in CPAM patients is estimated at 1%, but no long-term follow-up studies have yet been performed, while malignant degeneration may possibly occur at an older age [4,15,23]. Still, AIS often occurs in young adults and is characterized by a lepidic growth pattern, referring to spread along alveolar or cystic spaces [24]. Due to this growth pattern, mucinous AIS is often asymptomatic and detected in a late stage with multifocal, irresectable lesions which have a poor recurrence-free survival and prognosis [25,26].

The use of CT to predict histopathological outcome is increasingly being reported in other diseases and utilizing objective, quantitative scoring methods increase the reliability [27,28]. Previous research on the CT-pathology correlation in CPAM, has primarily focused on the diagnosis of the CPAM subtype [29–35]. In our current study we aimed to investigate if CT- imaging characteristics can be used to predict histopathological features, by using an objective quantitative CT scoring method.

2. Methods

The institutional review board approved this study and waived informed consent (MEC 2018-1355, MEC 2018-1164). We included all patients who underwent surgery in the Erasmus Medical Center, between January 1999 and March 2019, with a histologically confirmed CPAM diagnosis and a pre-resection volumetric inspiratory CT-scan of sufficient quality. The histological diagnosis of CPAM was defined by the occurrence of typical cystic formations lined by bronchial epithelium with or without smooth muscle and cartilage tissue [20]. Hybrid samples meeting aforementioned histological criteria as well as systemic arterial blood supply, were also included. Patients were excluded if CT-scans did not allow reliable scoring, such as CT-scans with a slice thickness exceeding 3 mm, or with poor image quality, or a large pneumothorax [36].

Using a standardized approach, all CPAM samples were histologically re-assessed for diagnosis, presence of inflammation, and mucinous proliferation by two blinded, independent pathologists [20]. CPAM Type 1 was defined as cystic lesions lined by pseudostratified epithelium with abundant papillary infoldings and abrupt transitions to thinner alveolar spaces. Type 2 was defined as cystic lesions with multiple, uniform, thin-walled cysts lined by columnar epithelium. Hybrid bronchopulmonary sequestrations were defined as lesions conforming to previously stated criteria and including systemic arterial blood supply. Histological signs of inflammation included the presence of inflammatory cell types (lymphocytes, neutrophilic granulocytes and macrophages) in the samples. Mucinous proliferation was defined as a cluster of mucinous cells partially lining the cyst, without invasion of the cystic wall or surrounding parenchyma [20].

Clinical data were obtained from the electronic patient records and included neonatal data and information on the surgical procedure. In our center, we adhere to a wait-and-see policy for all CLA patients unless they exhibit symptoms, such as respiratory distress, recurrent infections or cardiac volume overload [36]. Lung disease on chest CT was quantified using the newly-developed congenital lung abnormality quantification (CLAQ) scoring method [36]. A square grid was overlaid on axial CT slices after which a top and bottom CT slice were identified in which a grid cell contained at least 50% lung tissue. Twenty equidistant axial CT slices were scored between these margins and grid cells were assigned a label, according to the abnormality within (Fig. 1). The relative percentages of each annotated abnormality was calculated. Seven hierarchical categories were scored with the highest priority assigned to cystic walls (CW), followed by lesional hypodensity (LHypoD), parenchymal hypodensity (PHypoD), lesional hyperdensity (LHyperD), parenchymal hyperdensity (PHyperD), consolidation (CONS) and lastly normal lung tissue. Composite scores were calculated for lesional and parenchymal abnormalities. Parenchymal scores included PHypoD, PHyperD and CONS, while the other scores, apart from healthy lung tissue, were considered lesional abnormalities. The scored CT parameters were used to predict presence of inflammation and mucinous proliferation on histology (Fig. 1). Additionally, a cut-off value was calculated for predicting previously mentioned histology parameters.

To explore potential differences in CT parameters between patients with CPAM and those with a mucinous adenocarcinoma *in situ*, CT-scans of a random subset of adult patients with histologically confirmed mucinous adenocarcinoma *in situ* were quantified using the CLAQ method as well (Fig. 1) [16,36]. These scans were scored in random order along with the CT-scans of the CPAM patients by a single, blinded, observer.

2.1. Statistical analysis

Statistical analysis was performed using SPSS (version 25, IBM Corp., Armonk, NY, USA) and RStudio (version 1.0.153, RStudio, Inc., Boston, MA, USA). We used the "glmnet", "Ridge" and "Rpart" packages for our analyses. Differences between groups were assessed using the Mann-Whitney-U test for continuous variables and Chi-square test for categorical variables. Ridge regression was performed to identify potential CT-imaging predictors for the presence of inflammation, MP or AIS when adjusting for all others and to correct for multicollinearity. Ridge regression is a form of penalized regression in which coefficients with unimportant terms are driven towards zero. The penalization parameter or ridge parameter was chosen using ten-fold cross validation and we used the lambda with the minimum mean cross-validated error for our ridge regression. Coefficients are thus slightly biased downwards, but have smaller standard errors and are therefore more precise [37]. The optimal cut-off value for percentage lesional abnormalities was defined as the value yielding the maximal Youden index in the receiver operating characteristic curve [38]. The two-tailed statistical significance was set at a p-value < 0.05, unless Bonferroni's correction for multiple testing was applied.

3. Results

We included 33 eligible CPAM patients with a pre-resection CT-scan. CPAM type 1 was diagnosed in 18 (55%) patients, type 2 in 11 (33%) and hybrid lesions in 4 (12%) patients (Table 1). Patients underwent surgery at a median age of 2 months and the median time between CT-scan and surgery was 1 month. The most common indication for resection were respiratory insufficiency (67%) and recurrent infections (24%).

Histological signs of inflammation were found in samples of 13 (39%) patients (Table 1, Fig. 2). In these patients, a significantly lower percentage was found for cystic walls (median 5 vs 14), lesional (median 0 vs 6) and parenchymal hypodensity (median 0 vs 0). Similarly for the composite scores, the percentage lesional (median 14 vs 38) and parenchymal (median 0 vs 2) abnormalities were significantly lower in patients with histological signs of inflammation. A multivariate logistic ridge regression found that a

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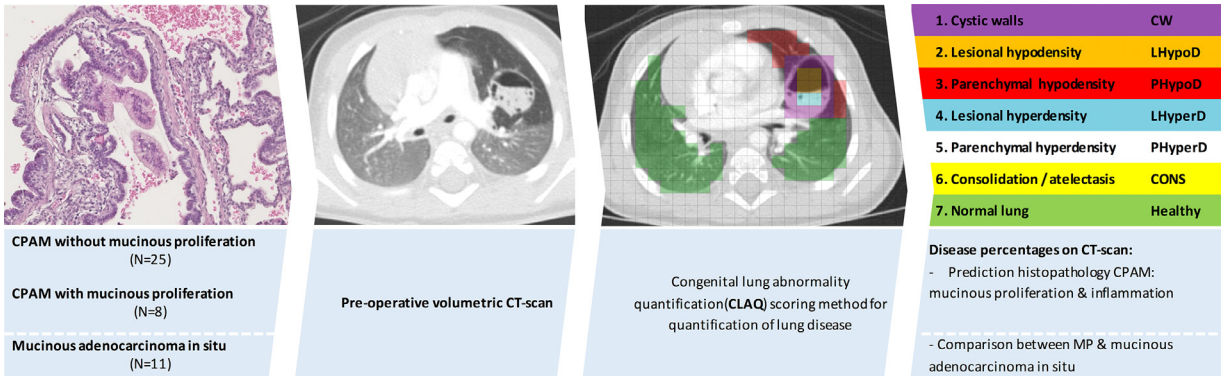

Fig. 1. Graphical display of study methods showing the histological image of a Congenital Pulmonary Airway Malformation (left), with adjacent coronal CT-image (middle), scored square grid according to the Congenital Lung Abnormality Quantification scoring method (middle), and explanation of hierarchical scored categories (right).

Table 1
Patient characteristics.

		Inflammation			Mucinous proliferation		AIS
		Yes	No		Yes	No	
		n = 13 (39%)	n = 20 (61%)		n = 8 (24%)	n = 25 (76%)	n = 11 (25%)
Male		7 (54)	12 (60)		4 (50)	15 (60)	
Gestational age at birth (weeks)		38.2 (34–40.6)	38.6 (34.7–42)		38 (36.6–40.6)	38.8 (34–42)	
Prenatal diagnosis		8 (67)	12 (60)		5 (63)	15 (63)	
Birthweight (grams)		3350 (1750–3840)	3283 (2616–4300)		3200 (2640–3960)	3348 (1750–4300)	
Diagnosis							
Congenital Pulmonary Airway Malformation 1		5 (38)	13 (65)		5 (63)	13 (52)	
Congenital Pulmonary Airway Malformation 2		5 (38)	6 (30)		3 (38)	8 (32)	
Hybrid bronchopulmonary sequestration		3 (23)	1 (5)		0 (0)	4 (16)	
Age at surgery (months)		1 (0-364)	15 (0-582)		13 (0-582)	1 (0-364)	
Reason resection				*			
Respiratory insufficiency		5 (38)	17 (85)		6 (75)	16 (64)	
Recurrent Infections		6 (46)	2 (10)		1 (13)	7 (28)	
Volume overload heart		1 (8)	0 (0)		0 (0)	1 (4)	
No symptoms		1 (8)	1 (5)		1 (13)	1 (4)	
Clinical sign of infection (pre-operative)		9 (69)	2 (10)	*	1 (13)	10 (40)	
Time between CT and resection (months)		1 (0–37)	6 (0–50)		2 (0–50)	0 (0–4)	
CLAQ score percentages							
Cystic walls	(%CW)	5 (0–53)	14 (2–73)	*	17 (3–53)	10 (0–73)	4 (1–18)
Lesional hypodensity	(%LHypoD)	0 (0–2)	6 (0–39)	*	1 (0–39)	0 (0–30)	0 (0–1) **
Parenchymal hypodensity	(%PHypoD)	0 (0–2)	0 (0–32)	*	0 (0–0)	0 (0–32)	0 (0-0)
Lesional hyperdensity	(%LHyperD)	0 (0–41)	0 (0–49)		15 (0–46)	0 (0–49)	0 (0–4)
Parenchymal hyperdensity	(%PHyperD)	0 (0–3)	0 (0–7)		1 (0–7)	0 (0–3) *	1 (0–6)
Consolidation	(%CONS)	0 (0–17)	0 (0–12)		0 (0–12)	0 (0–17)	0 (0–1)
Composite CLAQ score percentages							
Lesional abnormalities	(%Lesion)	14 (1–53)	38 (3–78)	*	54 (3–72)	17 (1–78) *	5 (1–18) **
Parenchymal abnormalities	(%Parench)	0 (0–17)	2 (0–32)	*	2 (0–19)	1 (0–32)	1 (0–6)
Total disease	(%Dis)	14 (1–53)	44 (6–84)	*	55 (6–79)	22 (1–84) *	9 (1–18) **

Data are presented as N (%) or median (range) . * p-value < 0.05. ** p-value < 0.05, between AIS & all 33 CPAM cases
CLAQ = Congenital Lung abnormality Quantification. AIS = Adenocarcinoma *in situ*.

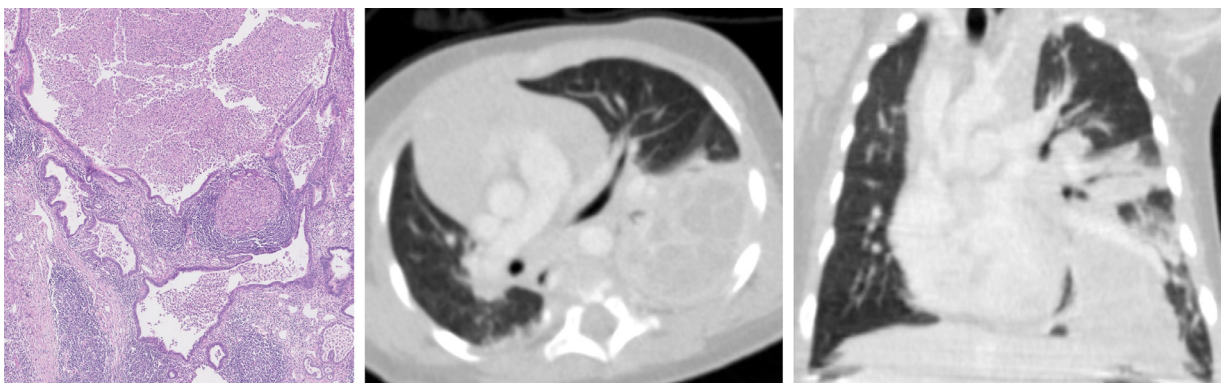

Fig. 2. Histological image of a congenital pulmonary airway malformation type 2 with signs of inflammation (left) and corresponding coronal and axial CT-images.

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Table 2
Ridge regression parameters.

	Inflammation			Mucinous proliferation			AIS		
	β	Exp(β)	*p*-value	β	Exp(β)	*p*-value	β	Exp(β)	*p*-value
(Intercept)	0.07	1.07	*NA*	-1.51	0.22	*NA*	-0.23	0.80	*NA*
Cystic walls	-0.01	0.99	*0.24*	0.00	1.00	*0.35*	-0.01	0.99	*0.59*
Lesional hypodensity	-0.02	0.98	*0.01*	0.00	1.00	*0.39*	-0.07	0.94	*0.07*
Parenchymal hypodensity	-0.02	0.98	*0.10*	-0.01	0.99	*0.25*	-0.06	0.94	*0.22*
Lesional hyperdensity	0.00	1.00	*0.81*	0.01	1.01	*0.10*	-0.04	0.96	*0.08*
Parenchymal hyperdensity	-0.05	0.95	*0.37*	0.11	1.11	*0.01*	0.52	1.69	*0.02*
Consolidation	0.02	1.02	*0.50*	0.01	1.01	*0.74*	-0.11	0.90	*0.35*
Percentage lesional abnormalities	-0.01	0.99	*0.04*	0.00	1.00	*0.02*	-0.03	0.97	*0.00*
Percentage parenchymal abnormalities	-0.01	0.99	*0.17*	0.00	1.00	*0.80*	-0.04	0.96	*0.29*

β = beta ridge regression coefficient. Exp(β) = exponential of beta
Significant *p*-values ($p < 0.05$) underlined.

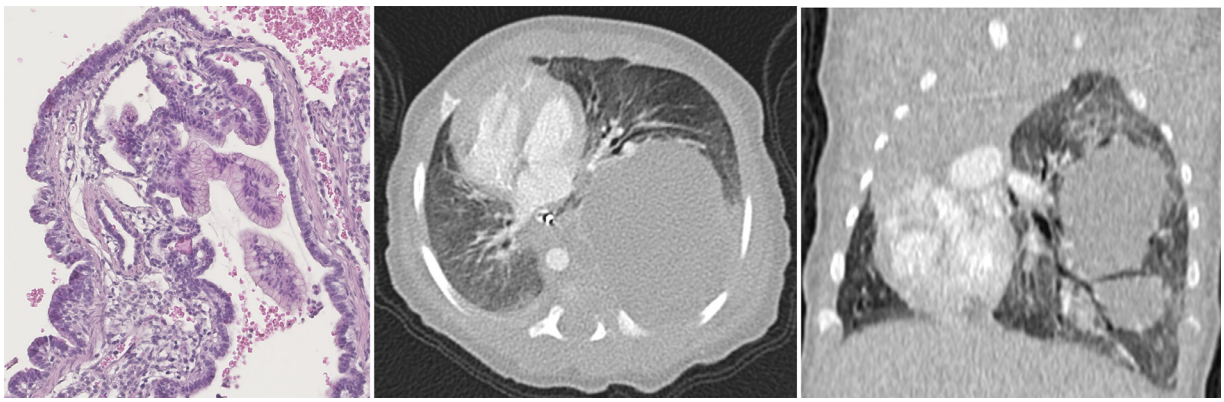

Fig. 3. Histological image of a congenital pulmonary airway malformation type 1 with mucinous proliferation (left) and corresponding coronal and axial CT-images.

lower percentage lesional hypodensity and lower percentage of lesional abnormalities are significant predictors for histological signs of inflammation (Table 2). In this cohort, an optimal cut-off value for disease percentage was found at 23% lesional abnormalities (sensitivity 70%, specificity 69%, accuracy 70%), in which the chance of inflammation is lower for lesions exceeding this value.

Mucinous proliferations were found in samples of 8 (24%) patients. A significantly higher percentage of parenchymal hyperdensity (median 1 vs 0) and a higher percentage lesional abnormalities (median 54 vs 17) was found in these patients (Table 1, Fig. 3). A multivariate logistic ridge regression found that a higher percentage of parenchymal hyperdensity and higher percentage of lesional abnormalities are significant predictors for the presence of MP (Table 2). In this cohort, an optimal cut-off value for disease percentage was found at 38% lesional abnormalities (sensitivity 88%, specificity 72%, accuracy 76%) in which the chance of MP is lower for lesions exceeding this value.

CT scans of eleven patients with a histological diagnosis of mucinous adenocarcinoma *in situ* (AIS) were scored using the CLAQ method. The median age at CT-scan was 70 years and no history of CPAM or other childhood lung disease was reported in the electronic patient records. Compared to the 33 CPAM patients, patients with AIS had a significantly lower percentage of lesional hypodensity (median 0 vs 1) and a lower percentage of lesional abnormalities (median 5 vs 29, Table 1, Fig. 4). A multivariate logistic ridge regression found that a higher percentage of parenchymal hyperdensity and a lower percentage of lesional abnormalities are significant predictors for AIS (Table 2).

4. Discussion

In this retrospective study, we aimed to identify CT-imaging features which may aid in predicting important histopathological findings in patients with a CPAM. We focussed on the most common reasons for surgical resection, specifically recurrent infections and potential for malignant degeneration as indicated by the presence of MP. We found that smaller lesions containing less air may be more prone to inflammation while larger lesions may be associated with the presence of MP.

Respiratory infections are more frequent in children with CPAM, compared to healthy children [39], and may lead to a decrease in lung function and endurance [11,40]. Due to this risk, early resection is thought to facilitate less complex surgery and postoperative compensatory lung growth [10]. However, in a follow-up study of 68 patients, pulmonary sequelae were reported in more than 50% of patients who have undergone surgery [41]. These conflicting findings emphasize the need for objective predictors to identify patients at high risk for developing inflammation. In our cohort, 39% of samples had histological signs of inflammation of which 69% showed clinical signs as well. Likewise, previous studies report histological signs of inflammation in 38% of asymptomatic patients [42] and 79% in symptomatic patients [12]. We found that the odds for histological signs of inflammation were increased in smaller lesions, especially those with less lesional hypodensity. This is a measure of air within the cysts which led us to hypothesize that less lesional hypodensity indicates smaller cysts. A previous study in patients with a small extralobar sequestration, found an increase in respiratory sequelae after resection, suggesting that small deviations in the airways may change normal airflow [41]. We speculate that a reduced airflow might cause stagnant debris which in turn leads to an inflammatory response and makes the lesion more susceptible to bacteria. This hypothesis is supported by a recent pilot study in which pathogenic microbes, which are known to play a role in chronic lung diseases with altered airflow and decreased lung clearance (*e.g.* asthma, COPD, and cystic fibrosis), are found in the lung microbiome of CPAM patients [43]. Smaller CPAM lesions containing less air may have an increased risk of inflamma-

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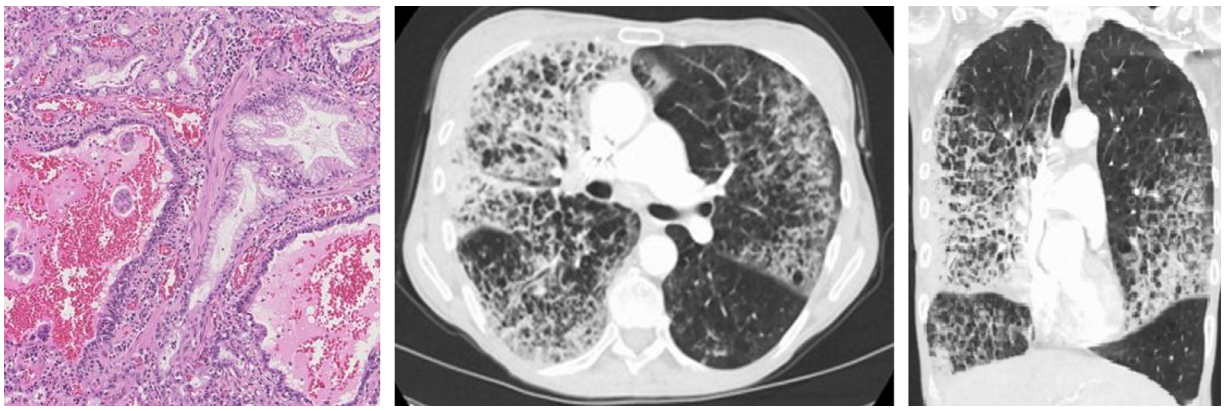

Fig. 4. Histological image of a mucinous adenocarcinoma *in situ* (left) and corresponding coronal and axial CT-images.

tion. Regular follow-up with focus on symptoms of respiratory infection may identify early symptoms.

An increasing number of studies report mucinous proliferations within CPAM tissue and some regard these lesions to be precursors of malignancy [15–19,21,22]. We found that lesions harboring MP were significantly larger and that the odds for MP increased with lesion size and percentage parenchymal hyperdensity. All studied MP samples contained a KRAS mutation [20], which are associated with proliferation and cell growth in lung cancer, but its significance in non-cancerous lung tissue is still unknown [44,45]. We speculate that lesions harbouring MP with a KRAS mutation may enlarge due to an increased proliferative potential. Increased parenchymal hyperdensity may be due to mass effect on the neighbouring parenchyma which causes ground-glass opacification. We found that lesions exceeding 38% of the volume of both lungs are at increased risk of harbouring MP. This percentage exceeds a single lung lobe, while most CPAMs have a sublobar extent [46]. The clinical significance and management of MP is still debated and because these lesions are small bland, they are often missed [15,47]. We therefore suggest awareness for MP during histopathological examination of lesions encompassing more than a single lung lobe with signs of mass effect on CT-imaging.

Lesions harbouring an AIS in adult patients were found to be smaller and the odds for AIS was increased for small lesions with increased parenchymal hyperdensity, which can be identified as ground-glass opacity on CT-scan. This finding is unsurprising as diffuse ground-glass opacity is the most common finding in patients with AIS [48]. A link between mucinous AIS and CPAM with MP is proposed and multiple studies report identical gene mutations [15,17,21–23]. Beside a lower percentage of lesional hypodensity, no other CT parameters were significantly different between AIS in adults and CPAM in our set, despite using a blinded approach and an objective scoring system. This similarity is concerning because AIS often presents with multifocal irresectable lesions with poor recurrence-free survival and prognosis [49]. Similarly, pleuropulmonary blastoma, an aggressive childhood lung tumor, cannot be radiologically distinguished from CPAM type 4 [50]. We suggest caution and close follow-up of small lesions with adjacent ground-glass opacification of the parenchyma.

Our study is limited by the small sample size while the use of a validated and objective quantitative CT-scoring method is a strength. Furthermore, histological features have been carefully reviewed but due to the inevitable sampling error, features may have been missed thus influencing the results. Additionally, in this cohort the 33 samples have been obtained from symptomatic patients versus the remaining 80 asymptomatic patients, which may have introduced a selection bias. Even though preliminary, our findings may help identify important biomarkers and should be validated in a larger prospective study with a long-term follow-up.

In conclusion, we found that in symptomatic patients, smaller CPAM lesions containing less air may be more susceptible to inflammation while lesions exceeding a single lung lobe with signs of mass effect may be associated with the presence of MP. Parenchymal hyperdensity is found as a predictor for MP as well as AIS and therefore should elicit either a more extensive gross sampling with use of additional histopathological markers or close follow-up, depending on the chosen management. We suggest caution and close follow-up of small lesions with adjacent ground-glass opacification of the parenchyma.

Conflicts of Interest and Source of Funding

We declare no conflicts of interest and this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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